

ALGINATE-BASED VACCINE COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to a composition and method for vaccinating vertebrate species. More particularly, this invention is directed to a vaccine composition comprising a preselected antigen in an alginate gel and a method of vaccinating using said composition to induce immunity.

BACKGROUND AND SUMMARY OF THE INVENTION

Historically, immunization has relied on the induction of humoral immunity by parental administration of vaccines. Antibodies induced by parental administrations however do not necessarily reach mucosal surfaces, the sites of entry of most infectious agents. Mucosal immunity, which develops at mucosal surfaces as a result of contact of antigen with mucosal lymphoid tissues, is an important first line of defense against infectious agents. Secretory immunoglobulin A (sIgA) is the predominant antibody isotype produced upon stimulation of the mucosa-associated immune system. sIgA prevents attachment of pathogens to the mucosal epithelium and neutralizes virus and bacterial toxins that can damage the host.

Induction of immunity at mucosal surfaces requires direct contact of antigens to a mucosal surface. However, this is not always possible or practical because of the handling/delivery problems or because the toxicity of the antigens to the mucosal surface. Mucosal immunity can be induced by the stimulating the mucosal associated lymphoid tissue (MALT), a network linking all mucosal sites to each other immunologically. Major concentrations of MALT are found in the upper respiratory tract (nasal associated lymphoid tissue) the lower respiratory tract (bronchus associated lymphoid tissue) as well as the gut associated lymphoid tissue. When the mucosa-associated lymphoid tissue of the gut or lung is exposed to an antigen, lymphocytes migrate to all other mucosal sites and produce antibodies.

The greatest accumulation of lymphoid tissue in the common mucosal immune system and in the body is the gut-associated lymphoid tissue (GALT) located in the intestines. Peyer's patches are specialized areas of GALT containing functional T and B lymphocytes, macrophages and antigen-presenting accessory cells. The lymphoid tissue is separated from the lumen of the gut by a layer of epithelial cells which are interspersed with antigen-presenting accessory cells. These specialized accessory cells actively internalize samples from the luminal space, and pass the samples to the underlying lymphoid cells. Exposure of GALT to antigen compounds triggers the clonal expansion of specific plasma (B lymphocyte) precursors and a population of memory lymphocytes which provide antibodies at a later time in response to the antigen. The antigen specific plasma precursors are influenced by CD3⁺ CD4⁺ and CD8⁺ T helper cells located between follicles to preferentially produce sIgA.

In contrast to the systemic lymphoid tissues of the body, the B lymphocyte population of GALT includes a significant population of cells which are committed to the synthesis of IgA class antibodies. This antibody type is not effectively induced through conventional intramuscular or subcutaneous immunization. The IgA committed B lymphoblasts migrate through the mesenteric lymph nodes resulting in enhanced immune responses in all mucosal sites including

the intestine, lung, mouth, eye, mammary gland, and the genitourinary tract. Thus, stimulation of GALT by oral vaccines can result in the prevention of infectious diseases at a variety of mucosal surfaces.

Orally administered vaccines are being studied intensively for delivery of vaccines for use in human diseases such as cholera, tetanus, influenza, and HIV using mice, guinea pigs, and baboons as experimental models. Development of vaccines for animals has a distinct advantage in that delivery systems and antigens can be tested for use in the target animal species for which the vaccines are intended. Hopefully, this will lead to quicker usage and acceptance of oral Vaccines. Information gained from oral vaccines developed for one species can be used for more efficient development of vaccines for other species. The development of RSV vaccines is an example where success in cattle could benefit humans and vice versa.

Oral administration of vaccines offers several advantages. Dosages could be administered to a large number of individuals via the food or water with minimal restraint and labor. Restraint also stresses animals rendering vaccination less effective thereby increasing the risk of infectious disease. Oral inoculation is quick and efficient. Formulations that could be used as one dose vaccines further eliminates the need for multiple handling of animals to administer subsequent booster inoculations. This is also an issue in human vaccination programs where compliance of patients to return to a medical center for second or third dose booster inoculations is poor. Adverse immune reactions following oral administration are also much less likely to occur and are therefore safer. For meat producing animals, oral administration has another advantage in that it avoids injection site reactions. Broken needles, contamination of the injection site, or the use of highly reactive adjuvants can induce abscesses that damage the carcass and the hides. These reactions decrease the value of the animal at slaughter.

Timely vaccination of livestock can be a critical aspect of effective farm management. Respiratory disease of viral and secondary bacterial etiology can spread rapidly through animal herds. Although stimulation of mucosal immunity can be achieved by intranasal administration or local injection into mucosal sites, such vaccination techniques typically require individual handling and restraint of each animal. Oral vaccination is a particularly cost effective way for livestock producers to vaccinate or treat a large number of animals at one time with minimal stress or labor. This is especially true when oral administration of the vaccine can be effected through ingestion by the animals during the course of feeding/drinking. Further, oral vaccines can be manufactured more cost effectively than parenterally administered vaccine formulations because of the fewer purification steps needed to generate an oral vaccine. Oral vaccination also offers the advantage of fewer side effects such as fever or other injection reactions.

Despite the advantages of oral vaccination, the development of oral vaccines has been delayed by the lack of adequate vaccine delivery systems. In the absence of suitable delivery systems, most oral vaccines, with the exception of cholera toxin (CT) and its nontoxic B subunit pentamer moiety, undergo degradation in the gastrointestinal (GI) tract resulting in limited absorption, which in turn results in insufficient immune responses.

Various delivery vehicles have been developed to deliver vaccine-relevant antigens to the gut-associated lymphoid tissues. Biodegradable polymers, such as poly(DL-lactide), poly(DL-lactide-co-glycolide) have been used to produce